

Title: Stabilized Interferon Compositions  
Inventor(s): Wolfe et al  
Application No: Not Assigned  
Atty Dkt No: PP16166.003(35784/240745)

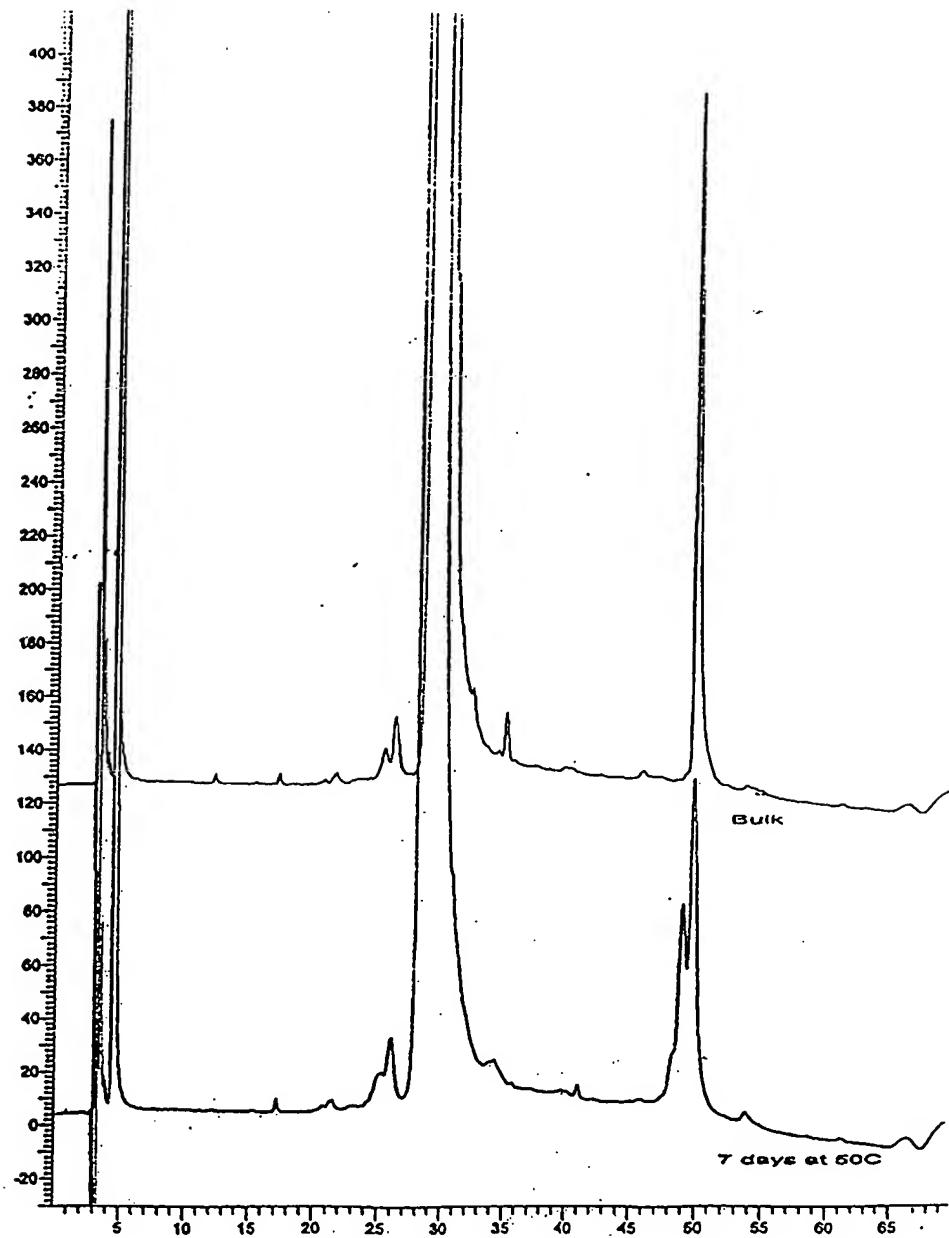


FIGURE 1

Title: Stabilized Interferon Compositions  
Inventor(s): Wolfe et al  
Application No: Not Assigned  
Atty Dkt No: PP16166.003(35784/240745)

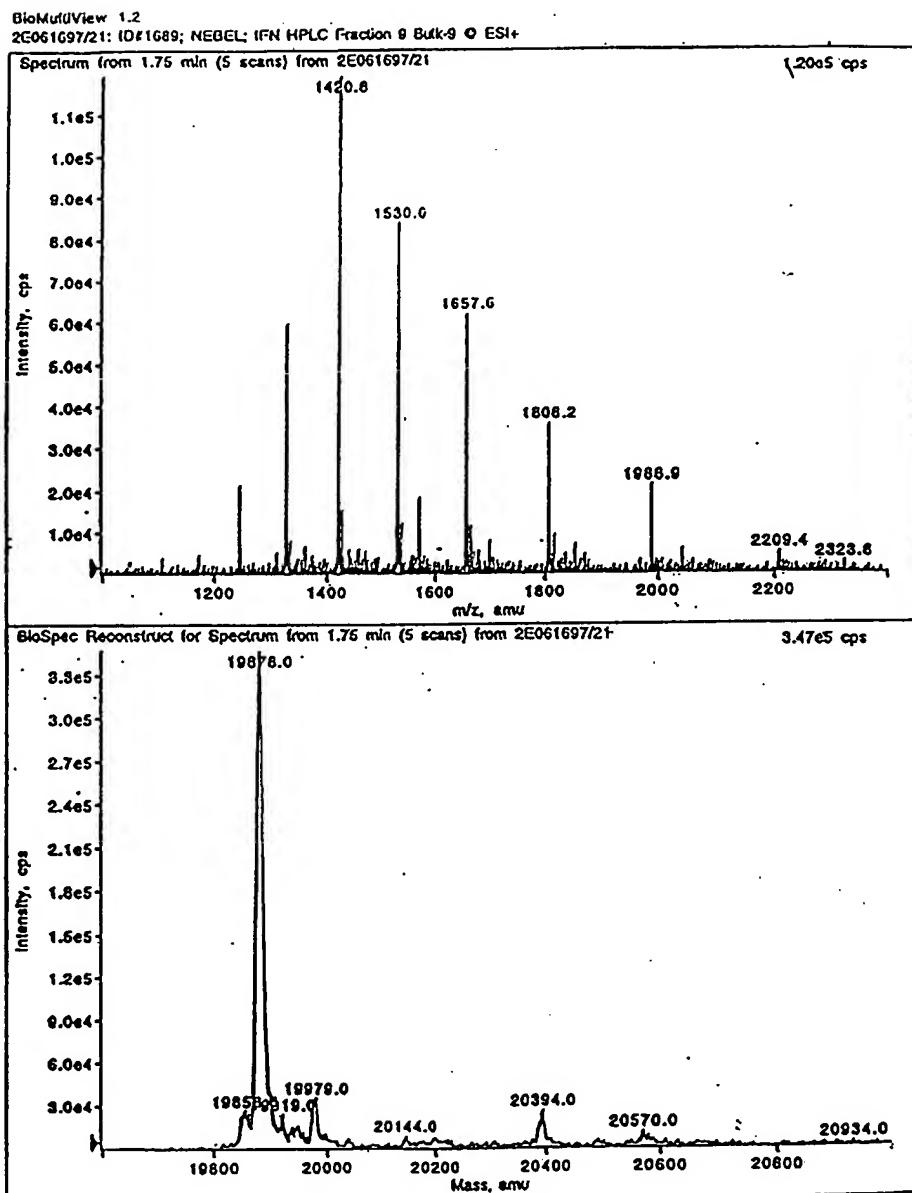


FIGURE 2

le: Stabilized Interferon Compositions  
entor(s): Wolfe et al  
Application No: Not Assigned  
Atty Dkt No: PP16166.003(35784/240745)

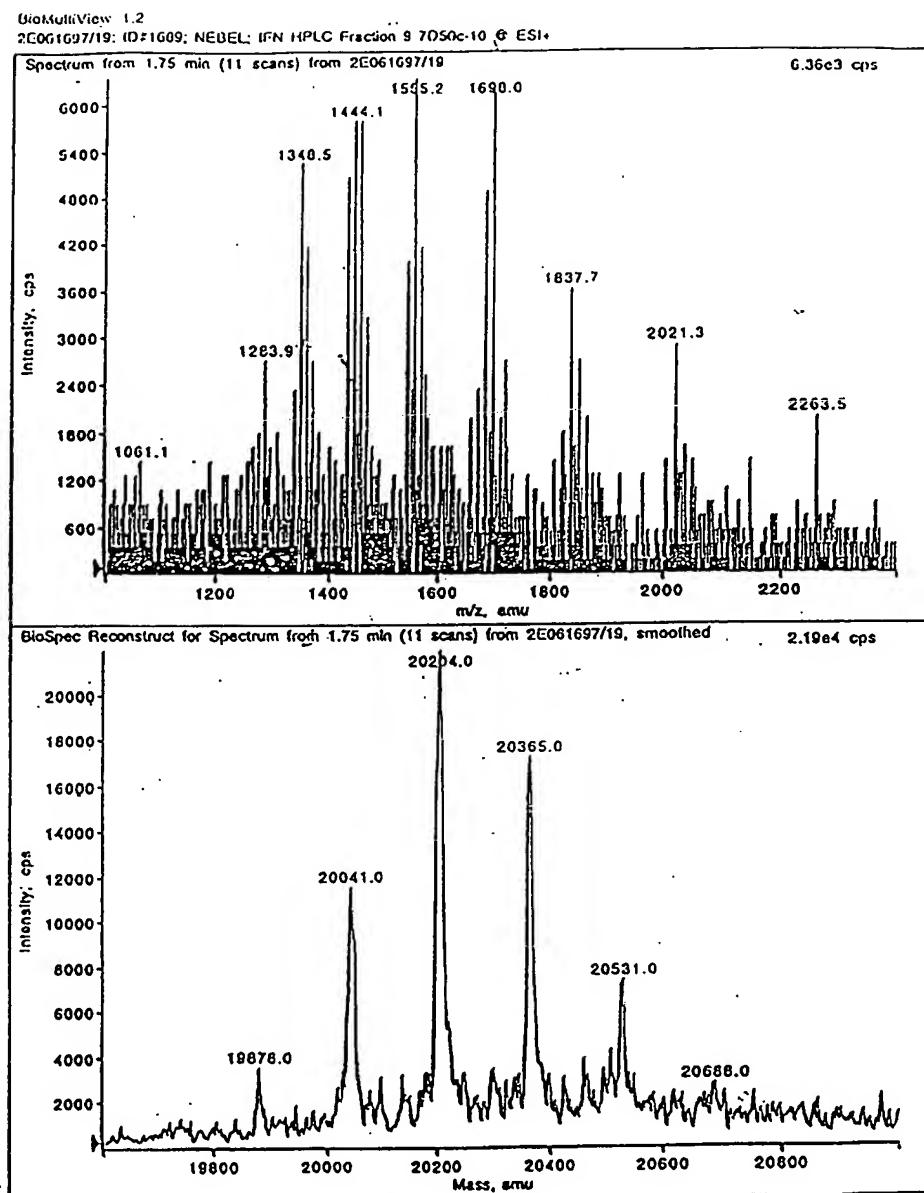


FIGURE 3

Title: Stabilized Interferon Compositions  
Inventor(s): Wolfe et al  
Application No: Not Assigned  
Atty Dkt No: PP16166.003(35784/240745)

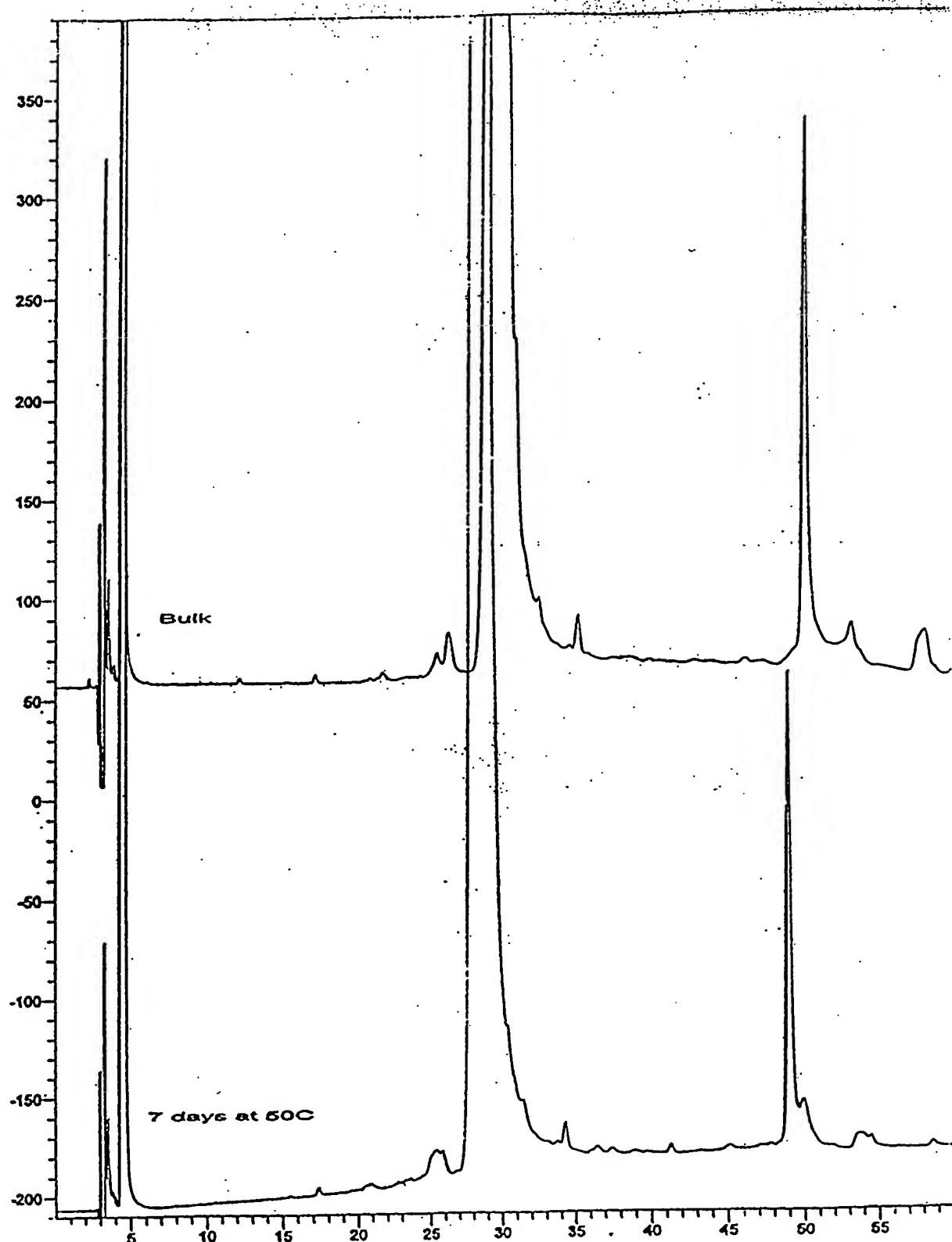


FIGURE 4

Title: Stabilized Interferon Compositions  
Inventor(s): Wolfe et al  
Application No: Not Assigned  
Atty Dkt No: PP16166.003(35784/240745)

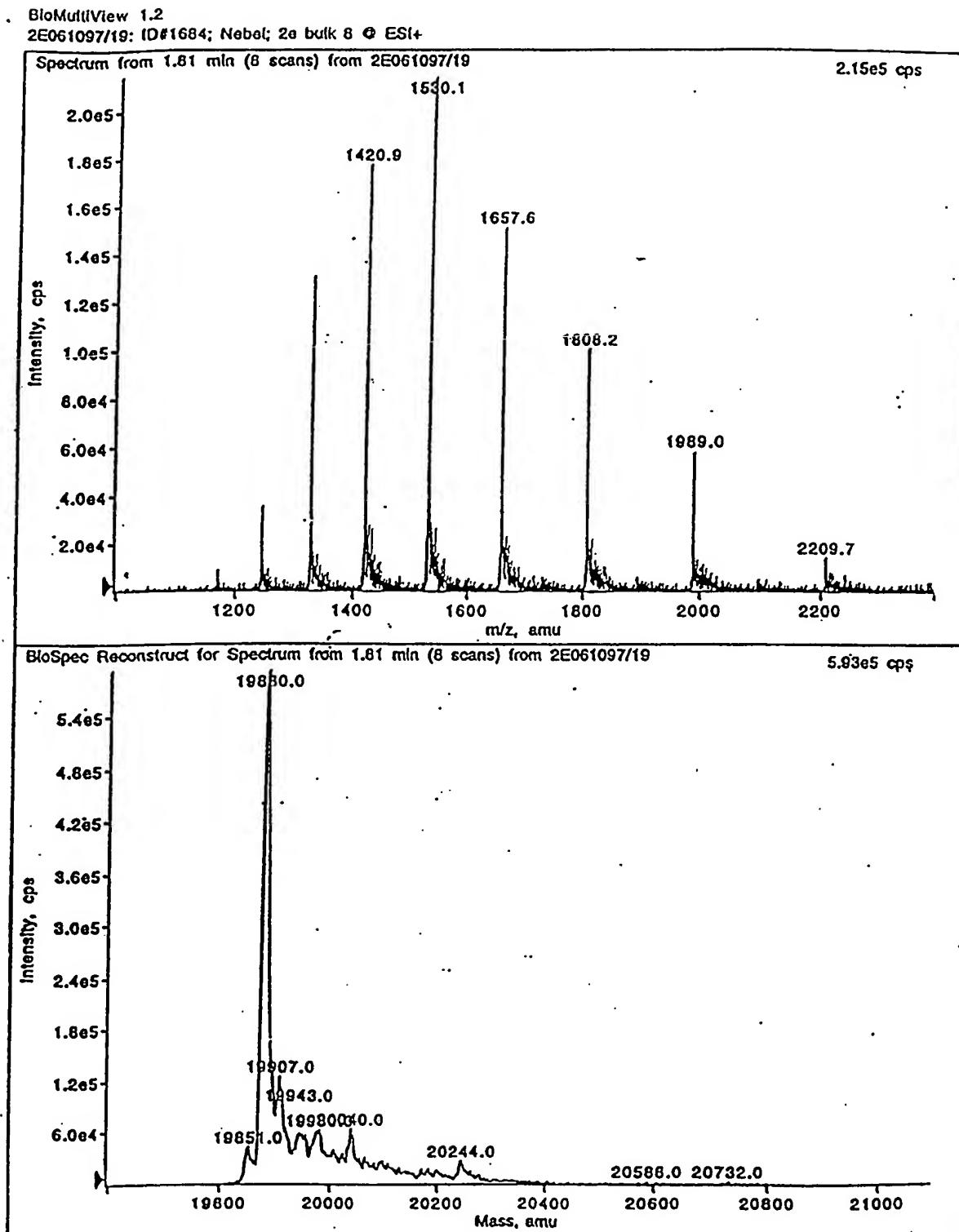


FIGURE 5

Title: Stabilized Interferon Compositions  
Inventor(s): Wolfe et al  
Application No: Not Assigned  
Atty Dkt No: PP16166.003(35784/240745)

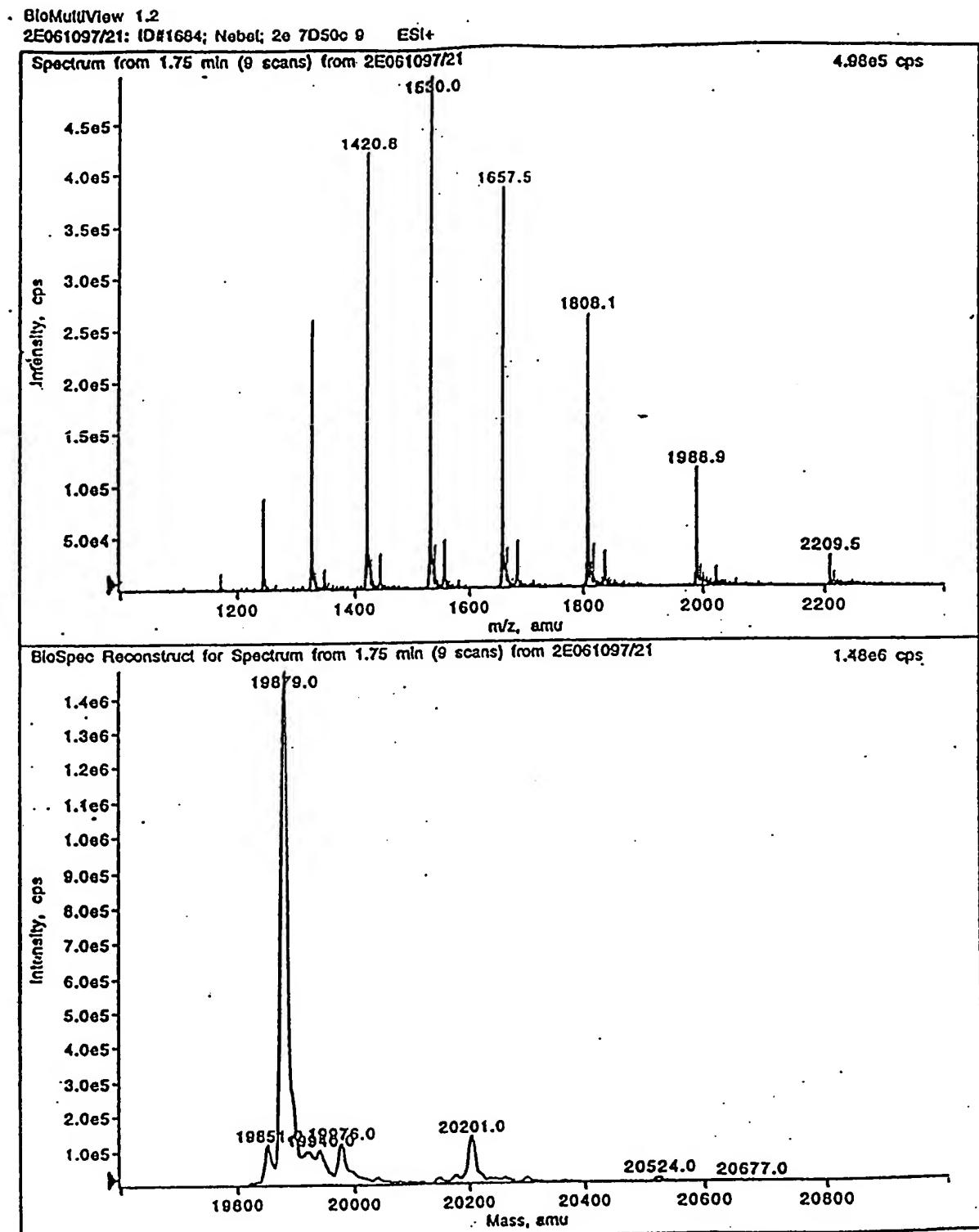


FIGURE 6

Title: Stabilized Interferon Compositions

Inventor(s): Wolfe et al.

Application No: Not Assigned  
Atty Dkt No: PP16166.003(35784/240745)

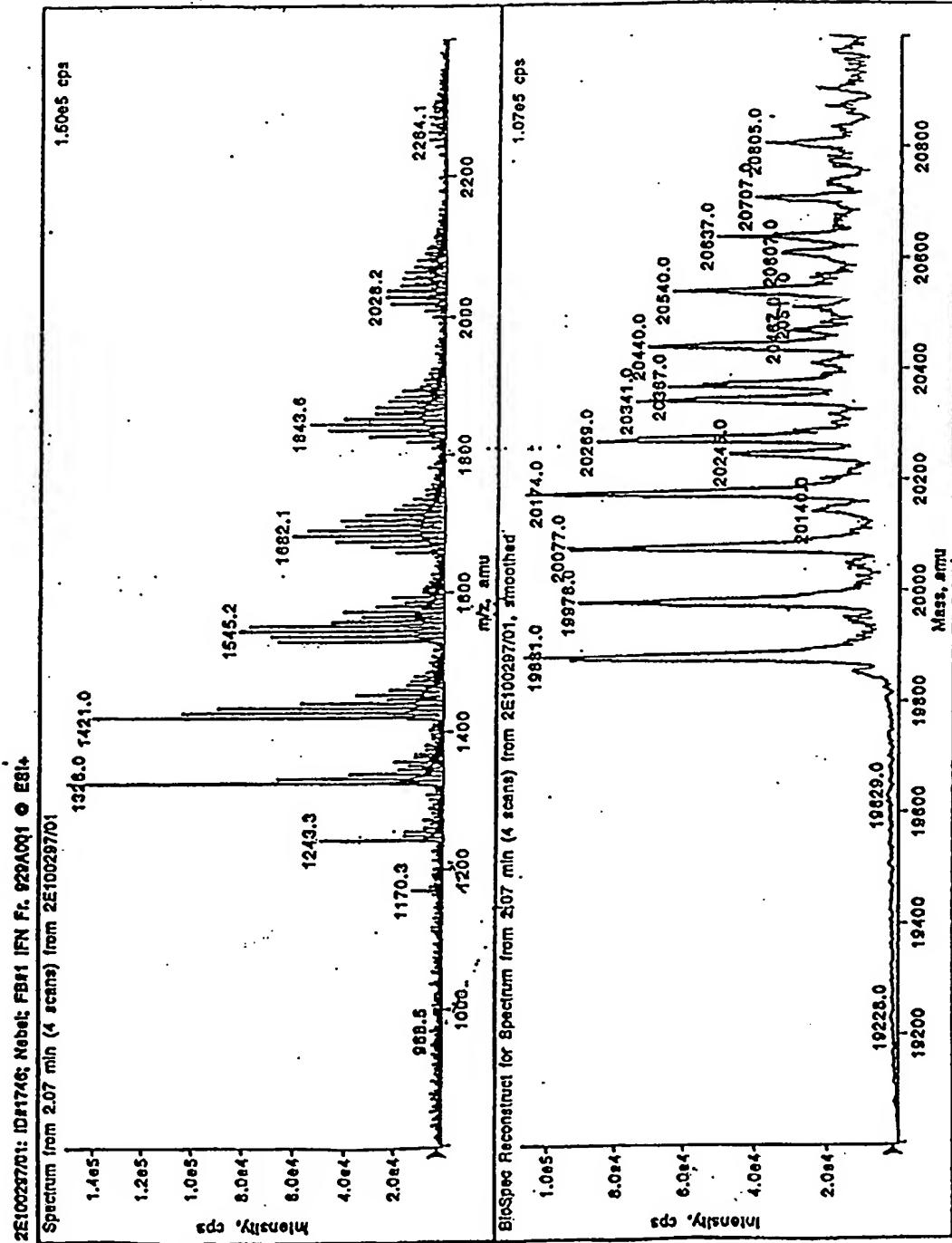


FIGURE 7

Title: Stabilized Interferon Compositions  
Inventor(s): Wolfe et al  
Application No.: Not Assigned  
Arry Dkt. No.: PP 16166.0035784/246443

BioMultiView 1.2  
2E10029704: IDM1746: Nebat: FBM4 IFN-1 929A004.Jaw • ESI+

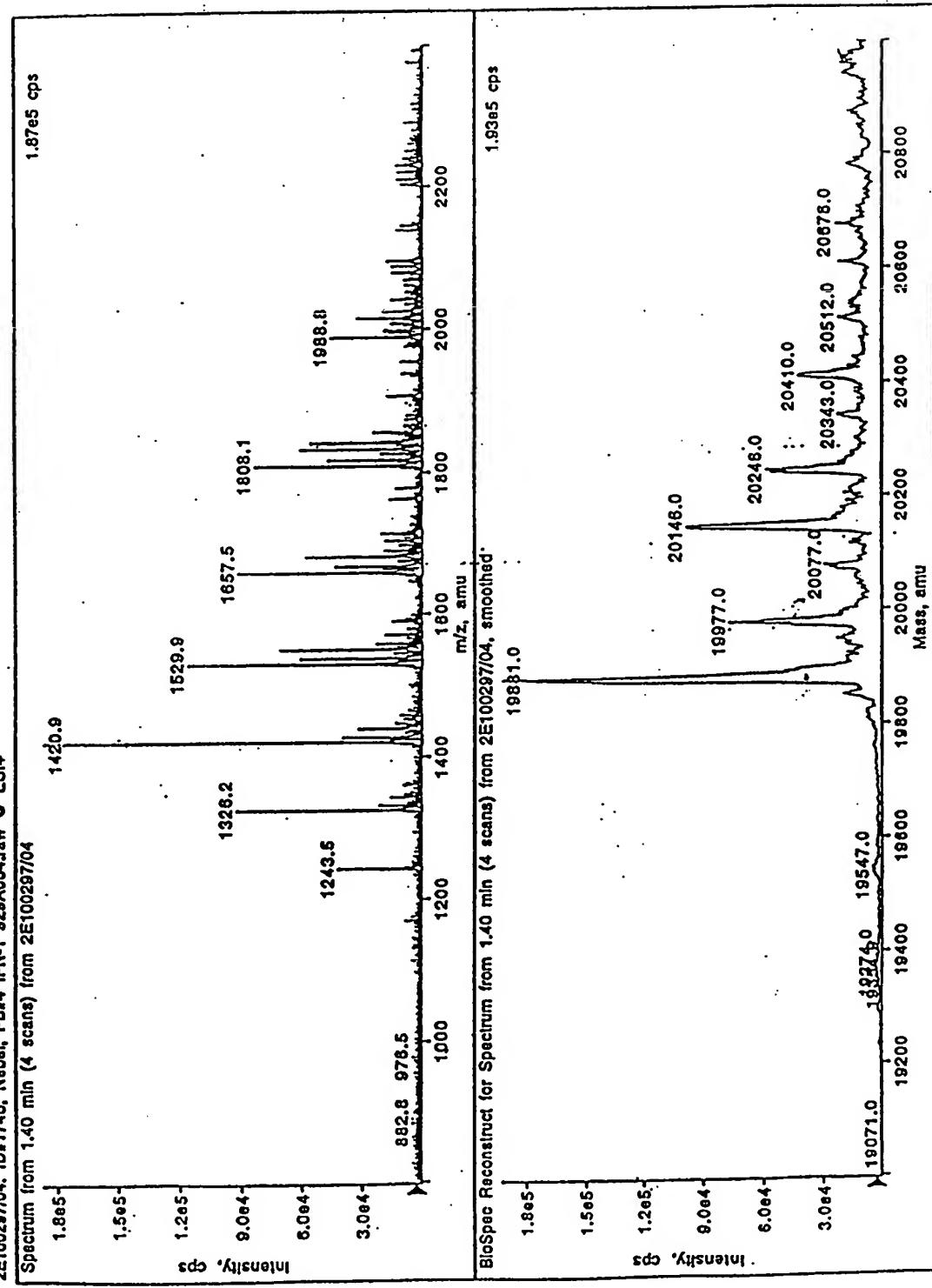


FIGURE 8

## Title: Stabilized Interferon Compositions

Inventor(s): Wolfe et al

THE JOURNAL OF CLIMATE

Attrib: Digit Nac: BBL16166\_003 (35781/240745)

Ally DKI No: FF10100.003(33/84/Z4U/43)

BioMultiView 12  
2E12229703 ID#1800; Nobel; IFN #14 184 0 ESI+

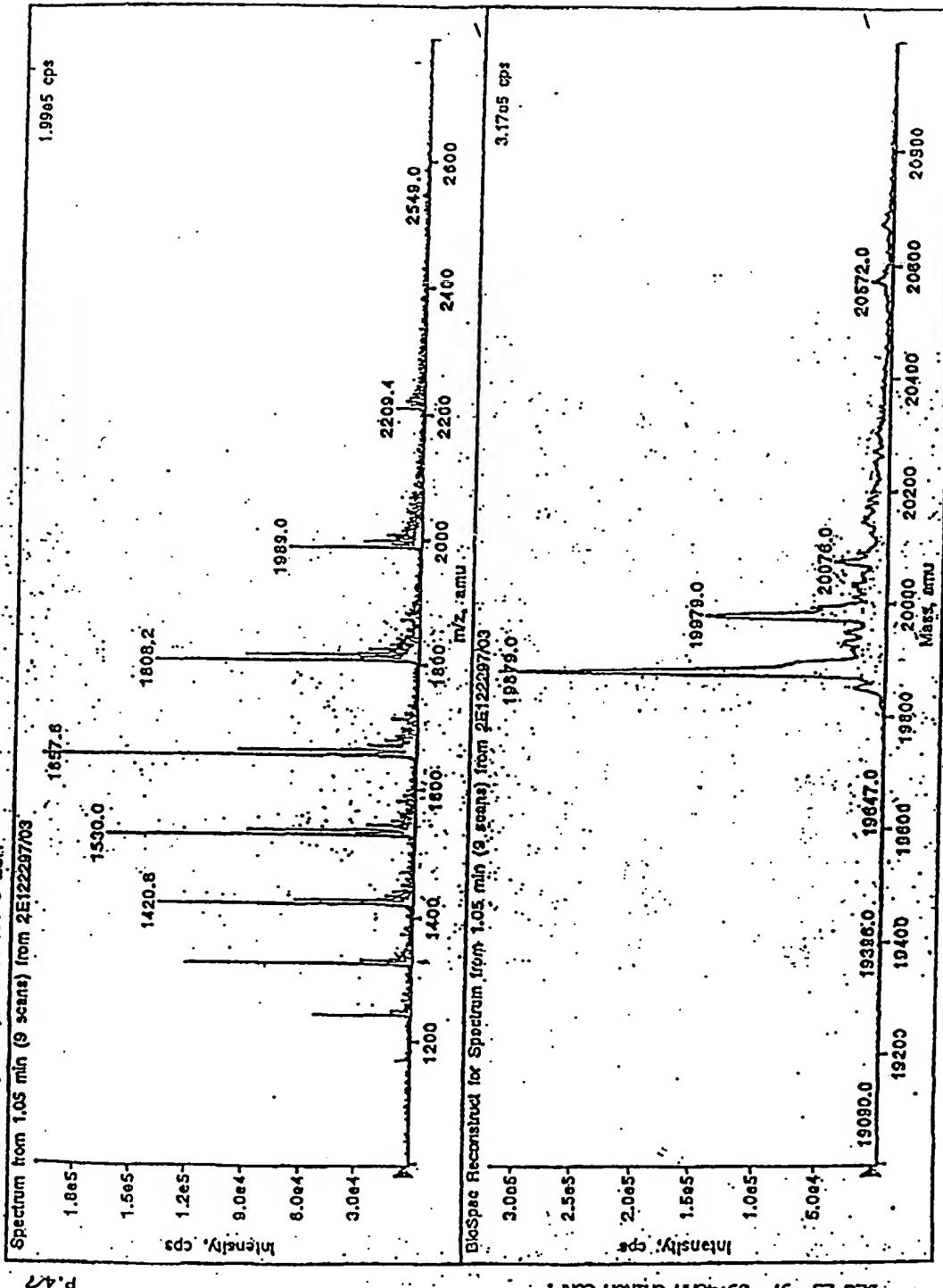


FIGURE 9

Title: Stabilized Interferon Compositions  
Inventor(s): Wolfe et al  
Application No.: Not Assigned

ATTY Dkt No 6186 P03135784/240745)

BioMultiView 1.2  
12/22/97.4:49:24, PN# ID#1800; Nebet IFN #16 M003 @: ESI+

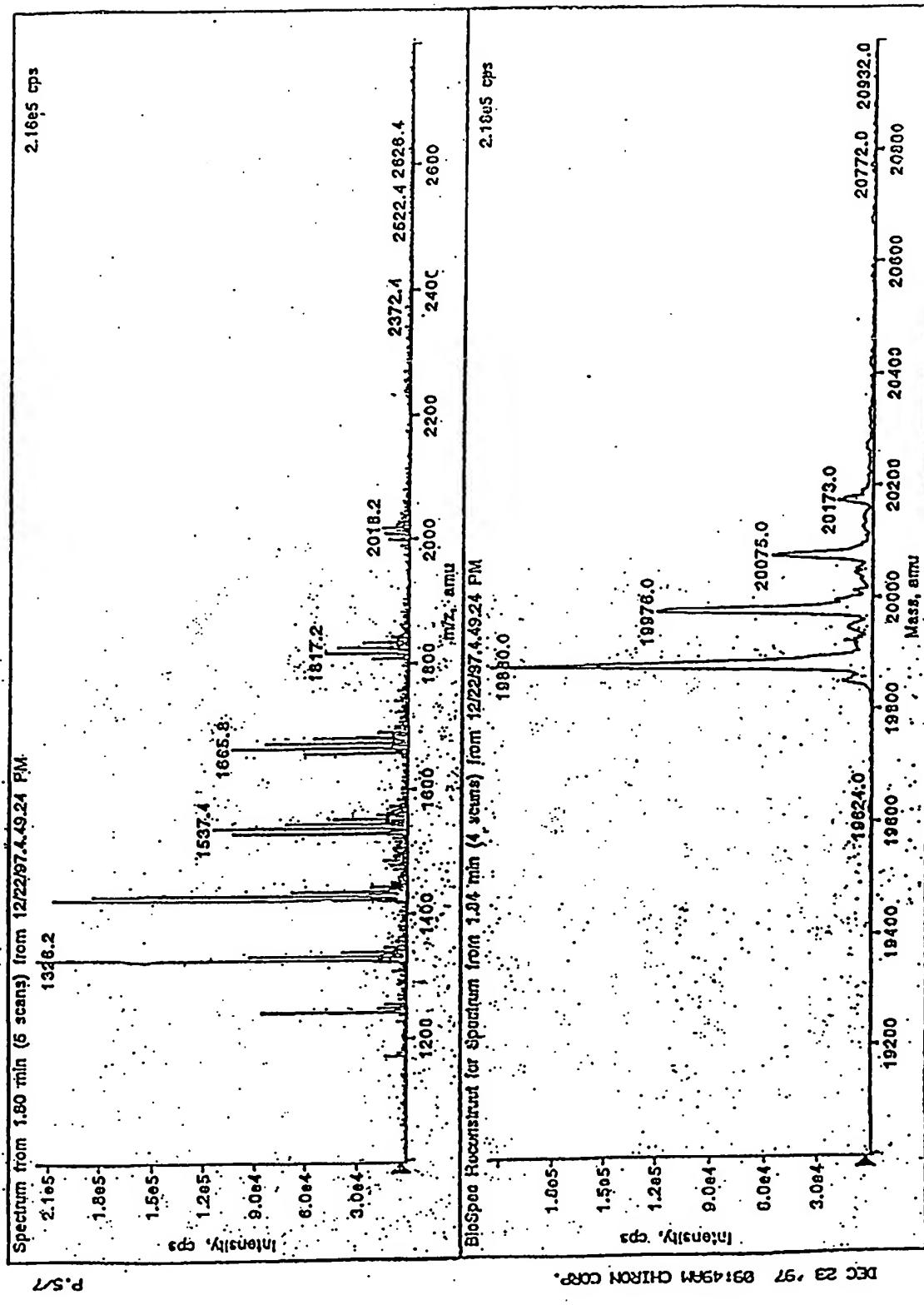


FIGURE 10

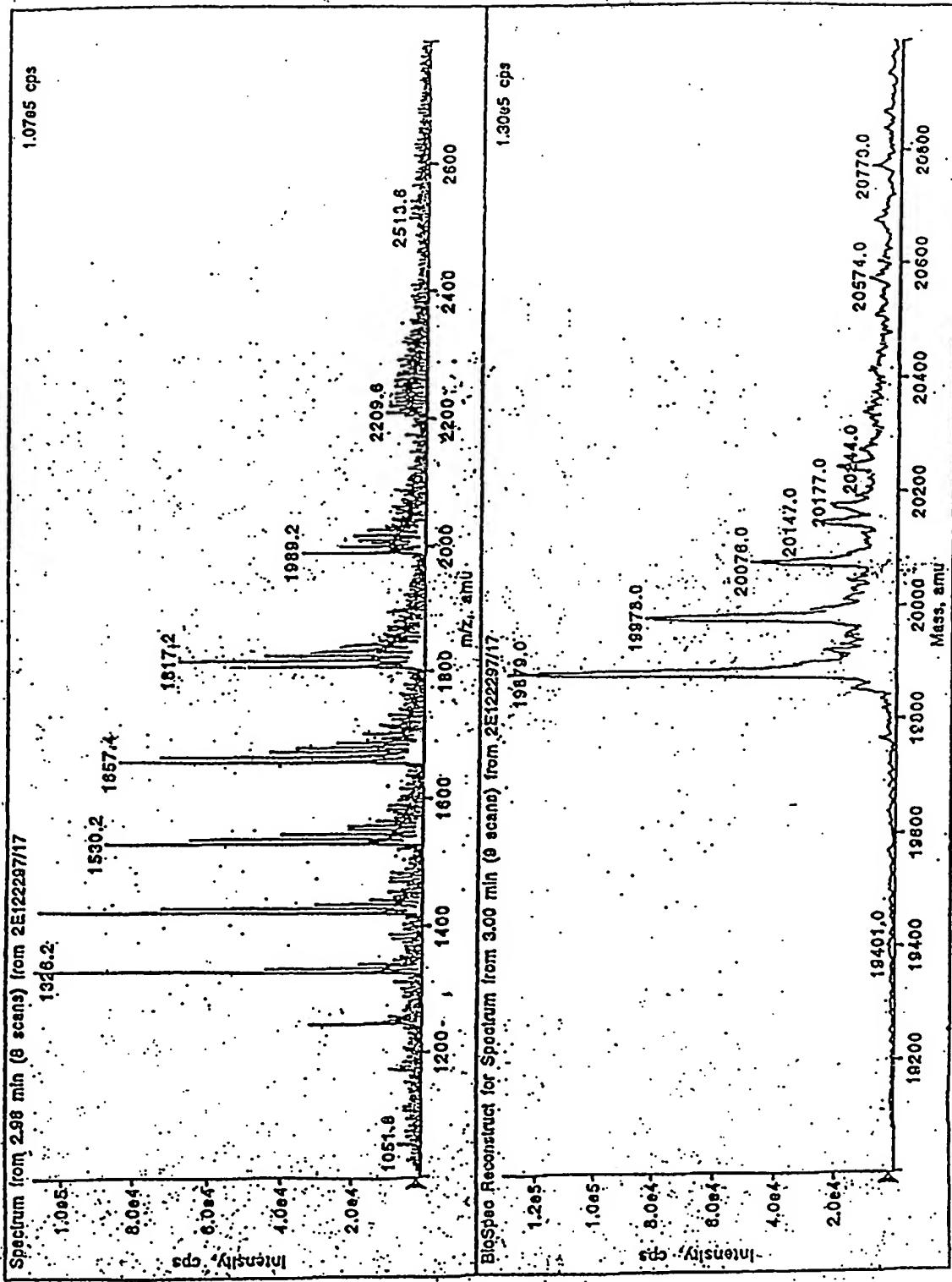
Title: Stabilized Interferon Compositions

Inventor(s): Wolfe et al

Application No: Not Assigned

Blaauw 12

2E122287/17: IDN1800: Nebel: IEN 117 5 0 ESI+



**FIGURE 11**

## STABILITY EVALUATION DATA

### Interferon- $\beta$ -1b: Dextrose Formulation

Product	Storage Temperature (upright, protected from light)	Months	Potency (Specific activity, IU/mg)	Glucosylated IFN- $\beta$ -1b concentration (mg/ml)	Total IFN $\beta$ -1b concentration (mg/ml)
IFN- $\beta$ 1b 0.25 mg/ml 1.25 % dextrose 1.25 % HSA  Lot: MBAPM023 7200-607	+ 8°C	0	$2.13 \times 10^7$	<0.02	0.22
	+ 8°C	1	$2.50 \times 10^7$	<0.02	0.23
	+ 8°C	2	$2.71 \times 10^7$	<0.02	0.23
	+ 50°C	2.2	$3.52 \times 10^7$	<0.02	0.23
	+ 50°C	2.5	$4.68 \times 10^7$	Too degraded	Too degraded
	+ 50°C	2.7	$4.60 \times 10^7$	Too degraded	Too degraded
	+ 50°C	3	$5.61 \times 10^7$	Too degraded	Too degraded
	+ 8°C	3	$2.41 \times 10^7$	<0.02	0.23
IFN- $\beta$ 1b 0.25 mg/ml 1.25 % dextrose 1.25 % HSA  Lot: MBAPM027 7200-600	+ 25°C	0	$2.12 \times 10^7$	<0.02	0.22
	+ 25°C	1	$2.05 \times 10^7$	<0.02	0.21
	+ 25°C	2	$3.24 \times 10^7$	<0.02	0.22
	+ 50°C	2.2	$3.88 \times 10^7$	<0.02	0.21
	+ 50°C	2.5	$4.64 \times 10^7$	Too degraded	Too degraded
	+ 50°C	2.7	$5.08 \times 10^7$	Too degraded	Too degraded
	+ 50°C	3	$5.91 \times 10^7$	Too degraded	Too degraded
	+ 25°C	3	$2.51 \times 10^7$	<0.02	0.23
IFN- $\beta$ 1b 0.25 mg/ml 1.25 % dextrose 1.25 % HSA  Lot: MBAPM027 7200-600	+ 37°C	0	$2.12 \times 10^7$	<0.02	0.22
	+ 37°C	1	$2.85 \times 10^7$	<0.02	0.18
	+ 37°C	2	$3.88 \times 10^7$	<0.02	0.23
	+ 50°C	2.2	$4.28 \times 10^7$	Too degraded	Too degraded
	+ 50°C	2.5	$4.88 \times 10^7$	Too degraded	Too degraded
	+ 50°C	2.7	$4.72 \times 10^7$	Too degraded	Too degraded
	+ 50°C	3	$5.44 \times 10^7$	Too degraded	Too degraded
	+ 37°C	3	$4.08 \times 10^7$	Too degraded	Too degraded

FIGURE 12

## STABILITY EVALUATION DATA

### Interferon- $\beta$ -1b: Highly Purified Mannitol Formulation

Product	Storage Temperature (upright, protected from light)	Months	Potency (Specific activity, IU/mg)	Glucosylated IFN- $\beta$ -1b concentration (mg/ml)	Total IFN $\beta$ -1b concentration (mg/ml)
IFN- $\beta$ 1b 0.25 mg/ml 1.25 % highly purified mannitol 1.25 % HSA	+ 8°C	0	$1.40 \times 10^7$	<0.02	0.22
	+ 8°C	1	$1.52 \times 10^7$	<0.02	0.21
	+ 8°C	2	$1.69 \times 10^7$	<0.02	0.22
	+ 50°C	2.2	$1.68 \times 10^7$	<0.02	0.22
	+ 50°C	2.5	$1.68 \times 10^7$	<0.02	0.21
	+ 50°C	2.7	$1.54 \times 10^7$	<0.02	0.21
	+ 50°C	3	$1.53 \times 10^7$	<0.02	0.22
	+ 8°C	3	$1.62 \times 10^7$	<0.02	0.23
IFN- $\beta$ 1b 0.25 mg/ml 1.25 % highly purified mannitol 1.25 % HSA	+ 25°C	0	$1.40 \times 10^7$	<0.02	0.22
	+ 25°C	1	$1.58 \times 10^7$	<0.02	0.21
	+ 25°C	2	$1.88 \times 10^7$	<0.02	0.22
	+ 50°C	2.2	$1.84 \times 10^7$	<0.02	0.22
	+ 50°C	2.5	$1.67 \times 10^7$	<0.02	0.20
	+ 50°C	2.7	$1.61 \times 10^7$	<0.02	0.21
	+ 50°C	3	$1.53 \times 10^7$	<0.02	0.22
	+ 25°C	3	$1.59 \times 10^7$	<0.02	0.23
IFN- $\beta$ 1b 0.25 mg/ml 1.25 % highly purified mannitol 1.25 % HSA	+ 37°C	0	$1.40 \times 10^7$	<0.02	0.22
	+ 37°C	1	$1.50 \times 10^7$	<0.02	0.21
	+ 37°C	2	$1.80 \times 10^7$	<0.02	0.21
	+ 50°C	2.2	$1.86 \times 10^7$	<0.02	0.21
	+ 50°C	2.5	$1.84 \times 10^7$	<0.02	0.20
	+ 50°C	2.7	$1.73 \times 10^7$	<0.02	0.20
	+ 50°C	3	$1.41 \times 10^7$	<0.02	0.20
	+ 37°C	3	$1.53 \times 10^7$	<0.02	0.22

FIGURE 13

**STABILITY OF BETASERON / BETAIFERON FINAL CONTAINER PRODUCT**  
**RESULTS FOR LOT MBDPANOS (MANNITOL FORMULATION)**

Storage Temp. (°C)	Mannitol Storage (cake)	Appearance			Residual Moisture (% by weight)	pH Upon Reconstitution	Potency (IU/kg $\times 10^7$ )	Container Closure Integrity	Sterility	
		Open Reconstitution	Open Recryst. Clarity	Open Recryst. Color						
0	white	clear, slightly yellow	-	-	0.3	7.4	23	-	Pass	
2	-	-	-	-	0.4	-	-	-	-	
3	white	clear, colorless	-	-	0.5	7.3	23	-	-	
4	-	-	-	-	0.4	-	-	-	-	
4	4	-	-	-	-	-	-	-	-	
4	5	-	-	-	-	-	-	-	-	
4	6	white	clear, colorless	-	0.4	-	-	-	-	
4	9	white	clear, colorless	-	0.5	7.3	34	-	-	
4	12	white	clear, colorless	-	0.5	7.4	31	-	-	
4	18	white	clear, slightly yellow	II	0.5	7.5	32	-	-	
4	24	white	clear, slightly yellow	II	>BY <sub>4</sub>	0.6	33	-	-	
30	2	-	-	-	0.7	-	-	-	-	
30	3	white	clear, colorless	II	<BY <sub>4</sub>	0.6	7.3	33	-	
30	4	-	-	-	-	0.6	-	-	-	
30	5	-	-	-	-	-	-	-	-	
30	6	white	clear, slightly yellow	II	BY <sub>4</sub>	0.7	7.4	31	-	
30	9	white	clear, colorless	II	<BY <sub>4</sub>	0.8	7.5	31	-	
30	12	white	clear, colorless	-	-	0.8	7.5	36	-	
30	18	white	clear, slightly yellow	II	colorless	1.0	24	28	-	
30	24	white	clear, slightly yellow	II	>BY <sub>4</sub>	1.1	7.4	33	Pass	
European Specifications:		White	Clear, colorless to light yellow	NMT Ref III	Colorless to slightly yellow NMT RX <sub>3</sub>	NMT 3%	7.1-7.8	22 to 45 x 10 <sup>7</sup>	Pass	Pass

FIGURE 14(A)

Title: Stabilized Interferon Compositions  
 Inventor(s): Wolfe et al.  
 Application No.: 10/6166.003  
 Assigned To: Allergan, Inc.  
 Atty Dkt No: PP16166.003(35784/240745)

**STABILITY OF BETASERON / BETAIFERON FINAL CONTAINER PRODUCT  
 RESULTS FOR LOT MBDPN006 (MANNTOL FORMULATION)**

Storage Temp. (°C)	Months In Storage	RP-HPLC Analysis		Peak B1 (Glucosylated) (mg/ml)
		Interferon beta-1b (Peak B + Peak B1) (mg/ml)	Peak B1 (mg/ml)	
4	0	-	-	-
4	2	-	-	-
4	3	-	-	-
4	4	-	-	-
4	5	0.24	<0.02	<0.02***
4	6	0.25**	<0.02***	<0.02***
4	9	0.23**	<0.02	<0.02
4	12	0.23	<0.02	<0.02
4	18	0.25	<0.02	<0.02
4	24	0.25	<0.02	<0.02
30	2	-	-	-
30	3	-	-	-
30	4	-	-	-
30	5	0.23	<0.02	<0.02***
30	6	0.25**	<0.02***	<0.02***
30	9	0.23**	<0.02	<0.02
30	12	0.23	<0.02	<0.02
30	18	0.24	<0.02	<0.02
30	24	0.24	<0.02	<0.02
Expected Results:		0.25 ± 0.04		NMT 0.02

\*\*\* SOP QG162 (AKA QD52) was not followed: NLT one injection per test vial (two test vials per lot) was not performed.

FIGURE 14(B)

Title: Stabilized Interferon Compositions  
 Inventor(s): Wolfe et al  
 Application No. 44 assigned to  
 Atty Dkt No: PP16166.003(35784/240745)

**STABILITY OF BETASERON / BETAIFERON FINAL CONTAINER PRODUCT**  
**RESULTS FOR LOT MEDPN008 (MANNITOL FORMULATION)**

Storage Temp. (°C)	Months in Storage	Date	Appearance			Residual Moisture (% by weight)	pH Upon Reconstitution	pH Upon Reconstitution	CPE Bravery (Units x 10 <sup>7</sup> )	Container Closure Integrity	Strength
			Upon Reconst. Clarity	Upon Reconst. Color	(% by weight)						
0	white	clear, colorless	-	-	0.3	7.3	2.9	-	-	Pass	
2	white	clear, colorless	-	-	0.5	7.4	2.7	-	-	-	
3	white	clear, colorless	-	-	0.5	7.4	2.7	-	-	-	
4	white	clear, colorless	-	-	-	-	-	-	-	-	
5	white	clear, colorless	-	-	0.5	7.5	3.3	-	-	-	
6	white	clear, colorless	-	-	0.6	7.6	3.4	-	-	-	
9	white	clear, colorless	-	-	0.6	7.6	3.2	-	-	-	
12	white	clear, colorless	>II	colorless	0.6	7.5	2.8	-	-	-	
18	white	clear, colorless	>II	>IX <sub>7</sub>	0.6	7.6	3.3	Pass	Pass	Pass	
24	white	clear, slightly yellow	<II	-	-	-	-	-	-	-	
30	white	clear, colorless	<II	-	0.7	7.5	3.0	-	-	-	
30	white	clear, colorless	<II	-	0.7	7.5	3.0	-	-	-	
30	white	clear, slightly yellow	<II	-	0.6	-	-	-	-	-	
30	white	clear, colorless	<II	BY <sub>6</sub>	0.7	7.5	3.4	-	-	-	
30	white	clear, colorless	<II	>IX <sub>6</sub>	1.0	7.6	3.4	-	-	-	
30	white	clear, colorless	<II	-	0.9	7.6	3.2	-	-	-	
30	white	clear, slightly yellow	<II	colorless	1.0	7.6	2.9	-	-	-	
30	white	clear, slightly yellow	<II	>IX <sub>7</sub>	1.1	7.6	3.2	Pass	Pass	Pass	
Product Specifications:			white	Clear, colorless to light yellow	NMT Ref III	Colorless to slightly yellow BY <sub>5</sub>	NMT 3%	7.1-7.3	22 to 45 x 10 <sup>7</sup>	Pass	Pass

FIGURE 15(A)

Title: Stabilized Interferon Compositions

Inventor(s): Wolfe et al

Application No.: Not Assigned  
Atty Dkt No: PP16166.003(35784/240745)

STABILITY OF BETASERON / BETAIFERON FINAL CONTAINER PRODUCT  
RESULTS FOR LOT MBDPN008 (MANNITOL FORMULATION)

Storage Temp. (°C)	Months in Storage	RP-HPLC Analysis		Peak B1 (phenoxylated) (mg/ml)
		Interferon beta-1b (Peak B + Peak B1) (mg/ml)	Peak B1 (phenoxylated) (mg/ml)	
4	0	-	-	-
4	2	-	-	-
4	3	-	-	-
4	4	-	-	-
4	5	0.23	<0.02	<0.02***
4	6	0.24***	<0.02***	<0.02***
4	9	0.23***	<0.02	<0.02
4	12	0.23	<0.02	<0.02
4	18	0.24	<0.02	<0.02
4	24	0.25	<0.02	<0.02
30	2	-	-	-
30	3	-	-	-
30	4	-	-	-
30	5	0.23	<0.02	<0.02
30	6	0.24***	<0.02***	<0.02***
30	9	0.22***	<0.02***	<0.02***
30	12	0.22	<0.02	<0.02
30	18	0.23	<0.02	<0.02
30	24	0.23	<0.02	<0.02

Expected Results: 0.25 ± 0.04 NMT 0.02  
 \*\*\* SOP Q0162 (AKA Q1052) was not followed: NLT one injection per test vial (two test vials per lot) was not performed  
 Note: A correction was made to the 18 month data point for RP-HPLC.

FIGURE 15(B)

Title: Stabilized Interferon Compositions  
 Inventor(s): Wolfe et al.  
 Application No.: Not Assigned  
 Atty Dkt No: PP16166.003(35784/240745)

**STABILITY OF BETASERON / BETAIFERON FINAL CONTAINER PRODUCT  
 RESULTS FOR LOT MBDPN09 (MANNITOL FORMULATION)**

Storage Months in Temp. Storage (°C)	Plug (scale)	Appearance		Upon Recov. Color	Upon Recov. Clarity	Residual Moisture (% by weight)	PH Upon Reconstitution	CPE Bleachability (IU/mg x 10 <sup>7</sup> )	Container Closure Integrity	Dye Leak Test
		Open	Reconstitution							
0	white	clear, colorless	-	-	-	0.4	7.3	3.0	-	-
4	2	N/A	N/A	-	-	0.5	-	-	-	-
4	3	white	clear, colorless	-	-	0.5	7.3	2.9	-	-
4	4	N/A	N/A	-	-	0.5	-	-	-	-
4	5	N/A	N/A	-	-	-	-	-	-	-
4	6	white	clear, slightly yellow	-	-	0.4	7.3	2.3	-	-
4	9	white	clear, colorless	-	-	0.6	7.4	3.0	-	-
4	12	white	clear, colorless	-	-	0.5	7.4	3.1	-	-
4	18	white	clear, colorless	<II	-	0.5	7.5	2.9	-	-
4	24	white	clear, slightly yellow	<II	-	0.6	7.4	3.2	Pass	Pass
30	2	N/A	N/A	-	-	-	-	-	-	-
30	3	white	clear, colorless	-	-	0.6	-	-	-	-
30	4	N/A	N/A	-	-	0.6	7.3	3.2	-	-
30	5	N/A	N/A	-	-	0.6	-	-	-	-
30	6	white	slight, slightly yellow	-	-	-	-	-	-	-
30	9	white	clear, colorless	-	-	0.5	7.4	2.4	-	-
30	12	white	clear, colorless	-	-	0.7	7.5	3.2	-	-
30	18	white	clear, colorless	III	-	0.7	7.4	3.1	-	-
30	24	white	clear, slightly yellow	<II	-	1.0	7.4	3.1	-	-
European Specification		White	Clear, colorless to light yellow	NMT Rec III	NMT Rec II	NMT 3%	NMT 3%	7.1-7.8	2.2 to 4.5 x 10 <sup>7</sup>	Pass
						Colorless to slightly yellow NMT Rec I				

FIGURE 16(A)

Title: Stabilized Interferon Compositions  
 Inventor(s): Wolfe et al  
 Application No.: Not Assigned  
 Atty Dkt No.: PP16166.003(35784/240745)

**STABILITY OF BETASERON / BETAFERON FINAL CONTAINER PRODUCT  
 RESULTS FOR LOT MBDPN009 (MANNITOL FORMULATION)**

Storage Temp. (°C)	Month in Storage	RP-HPLC Analysis	
		Interferon beta-1b (Peak B + Peak B1) (mg/ml)	Peak B1 ( $\mu$ g/ml)
0	0	-	-
4	2	-	-
4	3	-	-
4	4	-	-
4	5	0.24	<0.02
4	6	0.25***	<0.02***
4	9	0.24***	<0.02***
4	12	0.23	<0.02
4	13	0.25	<0.02
4	24	0.25	<0.02
30	2	-	-
30	3	-	-
30	4	-	-
30	5	0.22	<0.02
30	6	0.25***	<0.02***
30	9	0.24***	<0.02***
30	12	0.23	<0.02
30	13	0.24	<0.02
30	24	0.24	<0.02

Expected Result:

0.25 ± 0.04

NMT 0.02

\*\*\* SOP Q3162 (AKA Q1032) was not followed; NLT one injection per test vial (two test vials per lot) was not performed.  
 Note: A correction was made to the 18 month data point for RP-HPLC.

FIGURE 16(B)

## REDUCING ACTIVITY IN MANNITOL SAMPLES

Sample No.	Sample	Reducing Activity Content (ppm)	Mean Value (ppm)
1	Sample # 1 Unpurified	53.7	44.1
2	Sample # 2 Unpurified	44.1	
3	Sample # 3 Unpurified	34.4	
4	Sample # 1 Methanol Treated	19.3	18.5
5	Sample # 2 Methanol Treated	19.2	
6	Sample # 3 Methanol Treated	17.0	
7	Highly Purified Mannitol # 1	10.5	10.2
8	Highly Purified Mannitol # 2	11.2	
9	Highly Purified Mannitol # 3	8.9	

FIGURE 17